# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
ROBERT L . BUCHANAN
DIKE , BRONSTEIN , ROBERT & CUSHMAN
IP PRACTICE GROUP OF EDWARDS & ANGELL , LLP
P.O.BOX 9169
BOSTON, MA 02209



**PCT**

**WRITTEN OPINION**

**(PCT Rule 66)**

| | | |
|---|---|---|
| Applicant's or agent's file reference<br>46943CIP2PCT | | Date of Mailing *(day/month/year)*<br>REPLY DUE<br>within 1 months/days from the above date of mailing |
| International application No.<br>PCT/US02/34727 | International filing date *(day/month/year)*<br>29 October 2002 (29.10.2002) | Priority date *(day/month/year)*<br>29 October 2001 (29.10.2001) |
| International Patent Classification (IPC) or both national classification and IPC<br>IPC(7): A61K 39/395; C07K 16/36 and US Cl.: 424/145.1, 130.1, 141.1, 158.1; 530/387.1, 388.24, 389.3 | | |
| Applicant<br>SUNOL MOLECULAR CORPORATION | | |

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

   **When?** See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

   **How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

   **Also** For an additional opportunity to submit amendments, see Rule 66.4.
   For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
   For an informal communication with the examiner, see Rule 66.6

   **If no reply is filed,** the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 29 February 2004 (29.02.2004) .

| | |
|---|---|
| Name and mailing address of the IPEA/US<br>Mail Stop PCT, Attn: IPEA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (703) 305-3230 | Authorized officer<br>Maher M. Haddad<br>Telephone No. (571) 272-1600 |

Form PCT/IPEA/408 (cover sheet)(July 1998)

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Applicant

SUNOL MOLECULAR CORPORATION

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Authorized officer
Maher M. Haddad
Telephone No. (571) 272-1600

**WRITTEN OPINION**

International application No.
PCT/US02/34727

## I. Basis of the opinion

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☒ the description:
pages 1-80, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 81-92, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-17, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE _____

☐ the claims, Nos. NONE _____

☐ the drawings, sheets/~~fig~~ NONE _____

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."*

WRITTEN OPINION

International application No.
PCT/US02/34727

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. STATEMENT

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 10-13, 21-42, 45-54 and 65-66 | YES |
| | Claims | 1-9, 14-20, 43-44, 55-64 and 67-72 | NO |
| Inventive Step (IS) | Claims | 10-13, 21-42, 45-54 and 65-66 | YES |
| | Claims | 1-9, 14-20, 43-44, 55-64 and 67-72 | NO |
| Industrial Applicability (IA) | Claims | 1-72 | YES |
| | Claims | NONE | NO |

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:
The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

**V. 2. Citations and Explanations:**
Claim 1-9, 14-20, 43-44, 55-64 and 67-72 lack novelty under PCT article 33(2) as being anticipated by WO 96/40921. The `921 publication teaches a humanized antibody that binds specifically to human tissue factor (TF) and the ability of the CDR-grafted antibody to inhibit factor X activation, provides a measure of the ability of the CDR-grafted antibody to inhibit the activity of human tissue factor (see page 19, lines 1-6 in particular). The `921 publication teaches that the CDR-grafted antibodies are capable of inhibiting human tissue factor wherein the CDRs are derived from a non-human monoclonal antibody against tissue factor and the FR and C regions are derived from one or more human antibodies (see page 8, line 29 through page 9, line 4 in particular). In addition, the `921 publication teaches that FR region can retain the human FR residue at residues 6, 17, 68, 73 and 78 of the heavy chain and residues 39, 41, 116 and 105 of the light chain. The `921 publication further teaches that the heavy chain constant region and the light chain constant region is the human IgG4 constant region and the human IgG4 Kappa constant region, respectively (see page 16, lines 10-14 in particular). Further, the `921 publication teaches active fragments of the CDR-grafted antibodies, and in particular Fab fragments and F(ab')2 fragments (see page 16, lines 14-25 and published claim 18, page 92 in particular). The `921 publication teaches that the CDR-grafted antibody wherein the antibody is a murine antibody (monoclonal) (see published claim 2, page 90). Furthermore, the `921 publication teaches a pharmaceutical composition comprising at least one CDR-grafted antibody capable of inhibiting human tissue factor and a pharmaceutically acceptable carrier (see published claim 36 in particular). Finally, the `921 publication teaches nucleic acids encoding the heavy and light chains of CDR-grafted antibodies capable of inhibiting human tissue factor wherein the CDRs are derived from a murine monoclonal antibody against tissue factor and the FR regions are derived from one or more human antibodies (see page 21, lines 21-26 in particular). Further, the `921 publication teaches a method of producing a CDR-grafted antibody capable of inhibiting human tissue factor. The method comprises constructing an expression vector containing a nucleic acid encoding the CDR-grafted antibody heavy chain and an expression vector containing a nucleic acid encoding the CDR-grafted antibody light chain, transfecting suitable host cells with the expression vectors, culturing the transfected host cells under conditions suitable for the expression of the heavy and light chains, and recovering the CDR-grafted antibody (see pg 19, lines 22-31 in particular). The `921 publication teaches that a method of inhibiting blood coagulation with the humanized antibody against TF (see page 25, line 25 through page 27, line 9). Finally, the `921 publication teaches a method of detecting tissue factor in a biological sample with the humanized antibody (see pg 40, under Example 5 in particular).

While the prior art teachings may be silent as to the "wherein factor X or IX binding to the complex and the FX or FIX activation by TF:VIIa are inhibited" in claim 1, " the antibody has a dissociation constant (Kd) for the TF of less than about 0.5 nM" in claim 2, " the antibody is further characterized by increasing blood clotting time by at least about 5 seconds as determined by a standard prothrombin (PT) clotting assay at an antibody concentration of < 15 nM" in claim 3 per se; the antibodies in the reference is the same as the claimed antibodies. Therefore these limitations are considered inherent properties. Specially, because FX binds to a catalytically active complex that includes tissue factor.

**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)

Since the office does not have a laboratory to test the reference humanized antibodies, it is applicant's burden to show that the reference antibody does not bind to the TF about equal to or greater than the antibody obtained from cell line H36.D2.B7 recited in the claim.

Claims 1-6, 8-9, 55-58 and 62 lack an inventive step under PCT Article 33(3) as being obvious over U.S. Application No, 5,223,427 A in view of Owens *et al* (1994). The `427 patent teaches monoclonal antibodies TF9-1B8, TF9-5B7, TF8-5C4, TF8-11D12 and TF8-21F2 that immunoreact with human Tissue factor (col., 32-35, examples 5-7, and col. 41, Example 14 in particular). The `427 patent further teaches a composition comprising the antibody that can be formulated into the therapeutic composition as neutralized pharmaceutically acceptable salt forms or in association with the required diluent; i.e., carrier or vehicle (see col., 23 lines 42-65 in particular). The claimed invention differs from the reference teaching only by the recitation of a humanized antibody, a Fab fragment, a F(ab')2 fragment or in claims 1-6, 8-9 and 55-58. Owens *et al* teach the modification of murine antibodies such as a Fab fragment, a F(ab')2 fragment or a humanized antibody using monoclonal antibody technology. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement -dependent cytotoxcity (see the entire document).

While the prior art teachings may be silent as to the "wherein factor X or IX binding to the complex and the FX or FIX activation by TF:VIIa are inhibited" in claim 1, " the antibody has a dissociation constant (Kd) for the TF of less than about 0.5 nM" in claim 2, " the antibody is further characterized by increasing blood clotting time by at least about 5 seconds as determined by a standard prothrombin (PT) clotting assay at an antibody concentration of $<15$ nM" in claim 3 per se; the antibodies in the reference is the same as the claimed antibodies. Therefore ""wherein factor X or IX binding to the complex and the FX or FIX activation by TF:VIIa are inhibited" in claim 1, " the antibody has a dissociation constant (Kd) for the TF of less than about 0.5 nM" in claim 2, " the antibody is further characterized by increasing blood clotting time by at least about 5 seconds as determined by a standard prothrombin (PT) clotting assay at an antibody concentration of $<15$ nM" in claim 3 are considered inherent properties. Specially because FX binds to a catalitically active complex that includes tissue factor. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by the `427 patent as humanized antibody, Fab and F(ab')2 fragments of the humanized antibody as taught by the Owens *et al*. One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications as taught by Owens *et al*.

Claims 10-13, 21-42, 45-54 and 65-66 meet the requirements of PCT Articles 33(2) and (3) because the specific humanize antibody that binds to human tissue are neither taught nor suggested in the prior art.

Claims 1-72 have industrial applicability under PCT Article 33(4) because the humanized antibody that binds to human tissue factor claimed therein can be made or sued in health care industry.

---------- NEW CITATIONS ----------

U.S. 5,223,427 A (EDGINGTON et al) 29 June 1993, see the entire document.

OWENS et al. The genetic engineering of monoclonal antibodies. Methods. 1994, Vol. 168, No. 2, pages 149-165.

U.S. 6,555,319 B2 (WONG et al) 29 April, 2003, see claims 28-39.